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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,521	02/14/2002	Piyasena Hewawasam	CT-2640-NP	8919

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EXAMINER

JONES, DWAYNE C

ART UNIT

PAPER NUMBER

1614

DATE MAILED: 05/21/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/075,521	HEWAWASAM ET AL.	
	Examiner Dwayne C Jones	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on \_\_\_\_.  
 2a) This action is FINAL.                  2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-6 is/are pending in the application.  
 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_ is/are allowed.  
 6) Claim(s) 1-6 is/are rejected.  
 7) Claim(s) \_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 11) The proposed drawing correction filed on \_\_\_\_ is: a) approved b) disapproved by the Examiner.  
     If approved, corrected drawings are required in reply to this Office action.  
 12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
 \* See the attached detailed Office action for a list of the certified copies not received.  
 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
 a) The translation of the foreign language provisional application has been received.  
 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                  | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____ . |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                         | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>4</u> . | 6) <input type="checkbox"/> Other: _____                                    |

**DETAILED ACTION**

**DETAILED ACTION**

***Status of Claims***

1. Claims 1-6 are pending.
2. Claims 1-6 are rejected.

***Information Disclosure Statement***

3. The information disclosure statement filed on April 8, 2002 has been reviewed and considered, see enclosed copy of PTO FORM 1449.

***Specification***

4. Applicants are reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The

disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

More specifically, the instant abstract states that the variables of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are defined below. However, the abstract does not delineate these variables. It is recommended that the word "below" be replaced with the phrase, --in the specification--.

### ***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 2, 5 and 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of migraine disorders, does not reasonably provide enablement for the broad functional recitation of "disorders responsive to opening of the KCNQ potassium channels". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount

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of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The instant invention is directed to disorders responsive to opening of the KCNQ potassium channels. The method comprises administering 1,3-diazines of formula I.

(2) The state of the prior art

The compounds of the inventions are 1,3-diazines of formula I.

(3) The relative skill of those in the art

The relative skill of those in the art of pharmaceuticals is high.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. Supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5<sup>th</sup> Cir. 1978); In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24 (CCPA

1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5 (BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art); In re Wright, 999 F.2d 1557, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or pharmaceutical activity of 1,3-diazines of formula I prior to filing of the instant invention was an unpredictable art.

#### (5) The breadth of the claims

The instant claims are very broad. For instance, claims 1 and 2 are directed to the plethora of compounds of formulas I. The breadth of claims was a factor in Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d (Fed. Cir.), cert. Denied, 502 U.S. 856 (1991). In the Amgen case, the patent claims were directed to DNA sequences that encoded amino acid sequences. Because a very small change in the amino acid sequence of a protein can result in a very large change in the structure-function activity of a protein and because the laws of protein folding are in such a primitive state,

predicting protein structure (and hence, activity) while knowing only the sequence of the protein is akin to predicting the weather for a date in the future.

(6) The amount of direction or guidance presented

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fischer, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575. In the instant case, given the unpredictability of the physiological or pharmaceutical activity of these 1,3-diazines to be effective in treating migraines is insufficient for enablement. The specification provides no guidance, in the way of enablement for using the 1,3-diazines of formula I for use under the broad functional recitation of disorders responsive to opening of the KCNQ potassium channels other than treating migraines. In addition, the specification does not provide any enablement of using the 1,3-diazines of formula I for use under the broad functional recitation of disorders responsive to opening of the KCNQ potassium

channels that could be employed in this invention other than for the treatment of migraines. The specification provides no guidance, in the way enablement for the compounds of formula I. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S. 5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

(7) The presence or absence of working examples

As stated above, the specification discloses using the 1,3-diazines of formula I for use under the broad functional recitation of disorders responsive to opening of the

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KCNQ potassium channels. However, the instant specification only has enablement for treating migraines rather than using the 1,3-diazines of formula I for use under the broad functional recitation of disorders responsive to opening of the KCNQ potassium channels.

(8) The quantity of experimentation necessary

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether "undue experimentation" is required to make and use the instant invention. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of the disorders that are embraced under the broad functional recitation of disorders responsive to opening of the KCNQ potassium channels that would be enabled in this specification.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 3 and 4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. It is unclear what is embraced by the term "migraine-like attack". More specifically, how does this alleged condition differ from a migraine? Consequently, this phrase renders the claims vague and indefinite.

9. Claims 2, 4 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 2, 4 and 6 recite the following limitations in claim 2. First, the variable of R<sup>2</sup> is optionally substituted with one or two C<sub>1-3</sub> alkoxy groups. Second, when the variable of R<sup>3</sup> is defined as "trifluoromethyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylmethyl, phenyl, amino, di(C<sub>1-3</sub>alkyl) amino and pyrrolidinyl", there is no support for these groups in claim 1. Third, when the variable of R<sup>4</sup> is defined as "furanylmethyl and C<sub>3-7</sub> cycloalkylmethyl" as well as the optional substitutents on these groups, there is no antecedent basis for these definitions in claim 1. Fourth, there is no support for variables R<sup>6</sup> and R<sup>7</sup> to be have the C<sub>1-6</sub> alkyl and phenyl groups optionally substituted. In addition, there is no support for combining variables R<sup>6</sup> and R<sup>7</sup> into heterocyclic groups.

11. There is insufficient antecedent basis for this limitation in the claim. It is recommended that claim 2 be converted into an independent claim in order to obviate these claim ambiguities.

#### ***Claim Rejections - 35 USC § 103***

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

13. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148

USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bos et al. of U.S. Patent 6,274,588. Bos et al. teach of the pharmaceutical composition of the 4-phenyl-pyrimidine derivatives of formula I, (see column 2, lines 38 and claims 1-10). In fact, these 1,3-diazinyl compounds are known to be useful in treating headaches, especially migraines, (see column 1, lines 29 and 30). In addition, the selection of a known material based on its suitability for its intended use supported a

prima facie obviousness determination in Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle." 325 US at 355, 65 USPQ at 301. See also In re Leshin, 227 F.2d 197, 125 USPQ 416 (CCPA 1960) (selection of a known plastic to make a container of a type made of plastics prior to the invention was held to be obvious). Consequently, it would have been obvious to the skilled artisan to utilize these known 1,3-diazinyl compounds in pharmaceutical compositions regardless of the functional recitations that are instantly incorporated in claims 5 and 6. One having ordinary skill in the art would have been motivated to utilize these known compounds of Bos et al. in any pharmaceutical composition.

16. Claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suto et al. of U.S. Patent No. 5,811,428. Suto et al. teach of the pyrimidine carboxamide compounds and their analogs as well as their pharmaceutical compositions, (see columns 3-8, and from column 10, line 27 to column 11, line 18 and claims 1-27). In addition, the selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle." 325 US at 355, 65 USPQ at 301. See also In re Leshin, 227 F.2d 197, 125 USPQ 416 (CCPA 1960) (selection of a known plastic to make a container of a type made of plastics prior to the

invention was held to be obvious). Consequently, it would have been obvious to the skilled artisan to utilize these known pyrimidine carboxamide compounds and their analogs in pharmaceutical compositions regardless of the functional recitations that are instantly incorporated in claims 5 and 6. One having ordinary skill in the art would have been motivated to utilize these known compounds of Suto et al. in any pharmaceutical composition.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (703) 308-4634. The examiner can normally be reached on Mondays through Fridays from 8:30 am to 6:00 pm. The examiner can also be reached on alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-

1235  
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Tech. Ctr. 1614  
May 16, 2003